et al. and further in view of **Haseltine** et al., **Kang** and **Rodman**. This rejection is respectfully traversed.

First of all, the Examiner contends that **Haseltine** et al. and **Kang** provide the complete nucleotide/amino acid sequence of the HIV-1 *tat* gene. Applicants respectfully disagree. Applicants reiterate that **Haseltine** et al. and **Kang** are not applicable as prior art because they do not teach or suggest anything about the HIV-1 *tat* gene.

Haseltine et al. disclosed HTLV-III/LAC tat_{III} gene that encoded the HTLV-III/LAV associated trans-acting factor (column 3, lines 21-23). HTLV-III/LAV is the human T cell leukemia virus III (column 1, lines 21-22). Human T cell leukemia virus III is not the same as human immunodeficiency virus type I (HIV-1) as claimed herein. These are two different viruses. The HTLV-III/LAC tat_{III} gene and the HIV-1 *tat* gene are two different genes from two different viruses. **Haseltine** et al. only taught the HTLV-III/LAC tat_{III} gene. **Haseltine** et al. did not teach or suggest the HIV-1 *tat* gene as claimed herein. Hence, **Haseltine** et al. is irrelevant as a prior art.

Kang disclosed baculovirus expression system capable of producing foreign gene proteins at high levels. **Kang** only taught the

rev (example 1), vif (example 2) and pol (example 3) proteins of HIV-1. **Kang** did not teach or suggest the HIV-1 *tat* gene. Therefore, **Kang** does not disclose anything that is relevant to the present invention.

Consequently, the relevant prior art is **Brey** et al. in view of **Georgiou** et al. and further in view of **Rodman**. **Brey** et al. disclosed attenuated strain of bacteria that express malarial antigens. **Georgiou** et al. disclosed recombinant DNAs that are suitable for the expression of heterologous antigen on the surface of an enteric microorganism. **Rodman** disclosed a natural human IgM antibody reactive against HIV-1 tat protein. Applicants submit that combining **Brey** et al., **Georgiou** et al. and **Rodman** would not lead one of ordinary skill in the art to the present invention.

The instant invention is drawn to an HIV-1 Tat-expressing attenuated bacterial host that can induce both cellular and humoral anti-HIV-1 immune responses. **Brey** et al., **Georgiou** et al. and **Rodman** did not teach or suggest an HIV-1 Tat-expressing bacteria can be used to induce anti-HIV-1 immune responses. Furthermore, neither did **Brey** et al., **Georgiou** et al. and **Rodman** teach or suggest an HIV-1 Tat-expressing attenuated bacterial host

can induce both cellular and humoral anti-HIV-1 immune responses as claimed herein.

The importance of inducing a cellular immune response for an HIV vaccine to be effective has become increasingly clear in the past few years. The CTL response exerts substantial pressure on HIV replication during both the primary and chronic stages of infections. It is postulated that if the CTL response is great enough infected cells can be killed before allowing the virus to mutate. (McMichael and Rowland-Jones 2001 (attached)) This hypothesis is supported by the consistent presence of a cellular immune response specific to HIV in highly exposed persistently seronegative (HEPS) cohorts. (Miyahira, Murata et al. 1995 (attached); Rowland-Jones, Dong et al. 1999 (attached); Kaul, Rowland-Jones et al. 2001 (attached); Rowland-Jones, Pinheiro et al. 2001 (attached); Li, Promadej et al. 2002 (attached)) Also HIV specific CTL responses have been detected in uninfected exposed health care workers and uninfected babies born to infected mothers ((Pollack, Zhan et al. 1997 (attached); Buseyne, Burgard et al. 1998(attached); Buseyne, Chaix et al. 1998 (attached); Riviere and Buseyne 1998 (attached); Wasik, Wierzbicki et al. 2000 (attached))

The Examiner contends that it would have been obvious to express the HIV-1 *tat* gene provided by **Rodman** as an Lpp-OmpA-Tat fusion protein as suggested by **Georgiou** et al. in the *S. typhimurium* expression system described by **Brey** et al. because **Brey** et al. teach that this system is useful for generating strong immune responses. However, **Brey** et al. only taught immune responses to malarial antigens. **Brey** et al. did not teach or suggest an immune response to the product of HIV-1 *tat* gene. Teaching on immune responses to malarial antigens cannot be generalized to immune responses against HIV-1 Tat protein because, *inter alia*, induction of cellular and/or humoral immune responses by a putative antigen cannot be predicated and ascertained until actual experiments are carried out in model animals. In the absence of a teaching related to inducing specific immune responses to HIV-1 Tat, the cited references do not provided one of ordinary skill in the art with the requisite expectation of successfully producing Applicants' claimed invention because induction of immune responses by HIV-1 Tat has to be determined empirically.

The Examiner also contends that the skilled artisan would have been motivated to combine the cited references to make an HIV-1 Tat-expressing bacteria because that would facilitate the

development of HIV-1 Tat-specific immunological reagents for diagnostic, immunological or biochemical assays. Applicants submit that the cited references do not teach or suggest development of HIV-1 Tat-specific immunological reagents for diagnostic, immunological or biochemical assays. Furthermore, the present invention is not related to development of HIV-1 Tat-specific immunological reagents for diagnostic, immunological or biochemical assays. The essence of the present invention is an HIV-1 Tat-expressing bacterial host that can induce both specific cellular and humoral immune responses against HIV-1. As discussed above, the cited references are deficient in teaching or suggestion related to this critical element of inducing specific anti-HIV-1 immune responses.

The Examiner further contends that "all of the components employed in the instant application have been disclosed in the cited references. Both the bacterial host and fusion protein had already been used to produce recombinant proteins. Viral transactivating proteins have been cloned, sequenced and expressed in disparate expression systems. Therefore, there was a reasonable expectation of success of sufficient motivation for combining the aforementioned references." Applicants respectfully disagree.

Initially, Applicants note that the mere fact that "all of the components employed by the applicants... were well-known in the prior art" is immaterial to a determination of obviousness under35 U.S.C. §103. It is established law that one may combine known prior art components into a novel, non-obvious composition.

Secondly, it appears that the Examiner is arguing for reasonable success in expressing viral transactivating protein as fusion protein in the disclosed bacterial host. However, the present invention is not drawn to such bacteria. The essence of the present invention is a recombinant bacterial host that can induce cellular and humoral immune responses against HIV-1. Even though it may be obvious to try to construct an HIV-Tat expressing bacterial host, it is not obvious from the combined teaching of **Brey** et al., **Georgiou** et al. and **Rodman** that such bacteria can induce both cellular and humoral anti-HIV immune responses as claimed herein. The cited references do not teach or suggest methods or reagents that can induce cellular and humoral immune responses against HIV-1. The cited references also fail to provide the requisite expectation of success because the induction of cellular and humoral immune responses against a specific antigen must be determined empirically.

See also the above discussion concerning the importance of inducing cellular immune responses.

In view of the above remark, **Brey** et al., **Georgiou** et al. and **Rodman** do not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed invention. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claims 1, 2, and 5-11 under 35 U.S.C. §103(a) be withdrawn.

Claims 1, 2, and 5-11 were rejected under 35 U.S.C. §103(a) as being unpatentable over **Hone** et al. in view of **Georgiou** et al. and further in view of **Haseltine** et al., **Kang** and **Rodman**. This rejection is respectfully traversed.

As discussed above, **Haseltine** et al. and **Kang** are irrelevant as prior art. Hence, the applicable prior art is **Hone** et al. in view of **Georgiou** et al. and further in view of **Rodman**.

Hone disclosed attenuated *Salmonella* vaccine vector containing expression vector encoding HIV-1 gp120 fusion protein. **Georgiou** et al. and **Rodman** have been discussed above. Applicants submit that combining **Hone** et al., **Georgiou** et al. and

Rodman would not lead one of ordinary skill in the art to the present invention.

The present invention is drawn to an HIV-1 Tat-expressing attenuated bacterial host that can induce both cellular and humoral anti-HIV-1 immune responses. **Hone** et al., **Georgiou** et al. and **Rodman** did not teach or suggest an HIV-1 Tat-expressing bacteria can be used to induce anti-HIV-1 immune responses. Neither did **Hone** et al., **Georgiou** et al. and **Rodman** teach or suggest an HIV-1 Tat-expressing attenuated bacterial host can induce both cellular and humoral anti-HIV-1 immune responses as claimed herein.

The Examiner contends that **Hone** et al. teach *Salmonella* that induce both mucosal and systemic HIV-1 gp120-specific immune responses. However, **Hone** et al. only taught antibody responses in mucosal tissue and in blood. **Hone** et al. did not teach or suggest induction of cellular immune response (e.g. T cell response) by the HIV-1 gp120 protein. Indeed, **Hone** et al. taught that the issue of inducing cellular anti-HIV-1 immune responses by *Salmonella* vaccine strain is unresolved because "presently there is no consensus on the vector configuration that optimizes the ability of *Salmonella* to induce foreign antigen-specific cytotoxic $CD8^+$ CTLs in

vivo." (page 206, left column, third paragraph). Again, note the discussion above concerning the importance of inducing cellular immune responses for development of effective HIV vaccines.

In contrast, the present application shows that an HIV-1 Tat-expressing bacterial host can induce both cellular and humoral anti-HIV-1 immune responses. Further, Applicants submit herein a Declaration that demonstrates attenuated *Salmonella* with the HIV epitope-containing plasmids can cause the induction of a cytotoxic CD8 T cell response. Applicants submit that even though various components of the present invention are disclosed in **Hone** et al., **Georgiou** et al. and **Rodman**, the cited references do not teach or suggest an HIV-1 Tat-expressing bacterial host can induce both cellular and humoral anti-HIV-1 immune responses as shown and claimed herein.

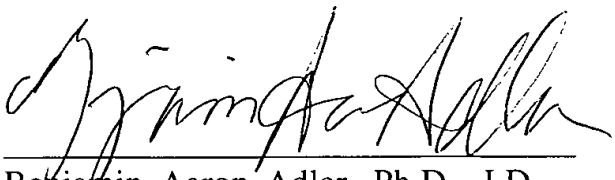
Similar to the discussion *supra* regarding **Brey** et al., **Georgiou** et al. and **Rodman**, Applicants submit that **Hone** et al., **Georgiou** et al. and **Rodman** do not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed invention in view of the lack of teaching and suggestion on possible induction of both cellular and humoral immune responses by an HIV-1 Tat-expressing

bacteria. Induction of cellular and/or humoral immune responses by a putative antigen cannot be predicated and ascertained until actual experiments are carried out in model animals. Thus, the invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claims 1, 2, and 5-11 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Final Office Action mailed September 10, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Mar 29, 2003



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